## REMARKS

### I. INTRODUCTION

In response to the Office Action dated October 9, 2002, claims 13-27 have been cancelled, claims 1, 5, 12 and 28 have been amended, and claims 50-52 have been added. These amendments to the claims and addition of the new claims do not introduce new matter. Claims 1-12, 28-29 and 50-52 remain in the application. Re-examination and re-consideration of the application, as amended, is requested.

### II. OBJECTIONS TO THE DISCLOSURE

At page 3 of the Office Action the disclosure was objected to because the Application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b).

As noted on page 3 of the outstanding Office Action, this application is a 371 of PCT/US00/25299 filed 09/17/1999. As shown by the attachment provided herein as Exhibit A, PCT/US00/25299 included an abstract of the disclosure as required by 37 CFR 1.72(b). Apparently this abstract has been misplaced. Applicants therefore provide a replacement abstract (provided as Exhibit B) and note that it is identical to the original abstract found in PCT/US00/25299. Accordingly, this replacement abstract does not introduce any new matter.

At page 3 of the Office Action the disclosure was objected to because the specification did not include the complete ATCC deposit information.

As noted hereinabove, the specification has been amended to include the complete ATCC deposit information.

### III. REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

#### A. Rejection of Claims 1-4, 28 and 29.

At page 4 of the Office Action, claims 1-4, 28 and 29 were rejected under 35 U.S.C. §112, first paragraph. In this rejection, the Examiner asserts that the specification, while being enabling for a human inflammatory breast cancer xenograft growing within lymphatic and blood vessel channels of an immunocompromised host, does not reasonably provide enablement for a human

inflammatory breast cancer xenograft growing within lymphatic and blood vessel channels of an immunocompetent host.

Applicants' respectfully traverse this rejection because one skilled in the art can determine whether the claimed invention can grow within lymphatic and blood vessel channels of an immunocompetent host without undue experimentation. In such situations, Courts have repeatedly stated that where some experimentation is necessary for the evaluation of an unpredictable characteristic (e.g. the ability of a cell to grow in a specific environment), the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. See e.g., *In re Angstadt and Griffin*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976), a case which organic species having an unpredictable activity were found to be enabled because their unpredictable activity could be evaluated without undue experimentation. In this context, Applicants similarly note that the level of skill in the relevant art is at a stage where artisans do not consider the amount of experimentation needed to evaluate a cell's ability to grow within lymphatic and blood vessel channels of an immunocompetent host to be undue.

While Applicants respectfully traverse this rejection, in order to facilitate the prosecution of the instant Application, claims 1 and 28 have been amended hereinabove to recite "A human inflammatory breast cancer xenograft, wherein the xenograft grows within lymphatic and blood vessel channels of an immunocompromised host". As the Examiner explicitly states that the specification is enabling for a human inflammatory breast cancer xenograft growing within lymphatic and blood vessel channels of an immunocompromised host, Applicants request the withdrawal of this rejection.

B. Rejection of Claims 1-4, 6-11, 28 and 29.

At page 7 of the Office Action, claims 1-4, 28 and 29 were rejected under 35 U.S.C. §112, first paragraph. In this rejection, the Examiner relies on Kleer et al. (Breast Cancer Res 2:423-429, 2000) which teaches that inflammatory breast cancer (IBC) represents about 5% of all breast cancers (abstract) and IBC tumors frequently lack expression of the cytosolic estrogen receptor (ER) (44% of IBC tumors are ER positive) and progesterone receptor (PgR) (30% of IBC tumors are PgR positive) (page 425, right col. third full paragraph), and about 58% of IBC tumors are EGFR positive (Kleer, page 426, left col. line 10) and over 70% of cases have a mutation in p53 (Kleer, page 426, left col. third full paragraph). In the rejection the Examiner notes that, according to Kleer,

the ER negative cases are about 56%, PgR negative cases are about 70%, EGFR positive cases 58% and P53 positive cases 30% in the population of IBC which is about 1-6% of all breast cancers.

In this context the Examiner rejects 1-4, 6-11, 28 and 29 under 35 USC 112, first paragraph and asserts that the practice of invention recited in these claims requires one skilled in the art to engage in an undue experimentation because "the chance of finding a patient who has IBC with all the claimed properties is very limited". In particular, the Examiner states that "[s]ince the xenograft with the properties is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The specification does not provide any source for obtaining the inflammatory breast cancer having the properties of the xenograft of claim 1 for establishing the xenograft".

Applicants respectfully traverse the rejection because, as illustrated below, a detailed analysis of the Kleer et al. reference shows that the data and disclosure information provided in this article supports the enablement of the invention recited in claims 1-4, 6-11, 28 and 29.

As noted by the Examiner in the outstanding Office Action, Applicants' specification teaches that the invention recited in the claims is derived from a patient diagnosed with a specific form of breast cancer known as inflammatory breast cancer (IBC). As illustrated by the Kleer et al. reference cited by the Examiner, IBC is a clinically and pathologically distinct form of breast cancer that is readily identified via a constellation gross, cytological and molecular characteristic. As explicitly noted at page 426 of this article, studies in this art shown that IBC cells (like the vast majority of cancer lineages) share a specific constellation of molecular characteristics, and, for example that "all of these studies have established that the majority of IBC tumors are ER and PgR negative, EGFR and c-erb positive, and have a rapid growth rate" (page 426, second full paragraph). Moreover, as IBC is categorized via a specific constellation of features, this is true with a variety of other molecules such as p53. For example, the Moll et al. article cited by Kleer et al. at page 426, teaches that p53 is expressed in the vast majority of IBCs (67% as shown in the Moll et al. article attached herein as Exhibit C).

As noted in the abstract of Kleer et al., approximately 5% of the breast cancers that are diagnosed annually in the USA exhibit the specific constellation of characteristics characterized as IBC. In this context, the article entitled "Cancer Statistics 2000" which is attached herein as Exhibit D teaches that approximately 182,800 cases of breast cancer in women are diagnosed annually in the

United States. A calculation using the 5% figure provided by Kleer et al. therefore shows that approximately 9,140 cases of breast cancer having the specific constellation of characteristics associated with IBC are diagnosed each year in the United States alone.

A skilled artisan familiar with both the Kleer et al. article and breast cancer statistics would understand that if the term "majority" as in "studies have established that the majority of IBC tumors are ER and PgR negative, EGFR and c-erb positive" (Kleer et al., page 426) is conservatively defined as 51%, then, according to Kleer et al. and cancer statistics, approximately 4,661 (51% of 9,140) new cases of ER and PgR negative and EGFR positive IBC are diagnosed each year in the United States. A skilled artisan would further note that **in the three years since the priority application was filed, approximately 13,984 new cases of ER and PgR negative and EGFR positive IBC were diagnosed in the United States alone**. An artisan would also likely note that if one wished to include those cases of IBC that are diagnosed annually in Canada, Europe, Japan etc. etc., the number of cases of IBC (sources from which the claimed invention could be generated) is **much much larger**. For these reasons, Applicants respectfully disagree with the Examiner's assertion that the subject matter recited in the claims is not enabled because "the specification does not provide any source for obtaining the inflammatory breast cancer having the properties of the xenograft of claim 1 for establishing the xenograft".

As illustrated above, one skilled in the art familiar with the Kleer et al. article and the breast cancer statistics simply could not agree with the Examiner's assertion that "the chance of finding a patient who has IBC with all claimed properties is very limited". The huge incidence of breast cancer among women makes the ready availability of IBC breast cancer tissue a sad but true fact. In this regard, Applicants hope that their disclosure will in some way contribute to a decline in the morbidity and/or mortality associated with IBC and are pleased to note that the Kleer article provides favorable commentary regarding the potential of the MARY-X xenografts recited in their claims (see Kleer et al. at page 428, first full paragraph).

For the reasons articulated above, Applicants' specification teaches the skilled artisan how to make the claimed invention without undue experimentation. Consequently, Applicants respectfully request the withdrawal of this rejection.

C. Rejection of Claims 5 and 12.

At page 10 of the Office Action, claims 5 and 12 were rejected under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As noted hereinabove, claims 5 and 12 have been amended to include the ATCC deposit information. Applicants state that the deposit of ATCC Accession No(s). PTA-2736 and PTA-2737 have been accepted by the American Type Culture Collection ("ATCC") at 10801 University Boulevard, Manassas, VA, an International Depository Authority under the provisions of the Budapest Treaty. All restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application, and the deposit will be replaced if viable samples cannot be dispensed by the depository. The material has been deposited under conditions that ensure that access to the material will be available during the pendency of the patent application to one determined by the Commissioner to be entitled thereto under 35 CFR §1.14 and 35 USC §122. The deposited material will be stored with all care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request for the furnishing of a sample of the deposited material, and in any case at least thirty (30) years after the date of a deposit or for the enforceable life of the patent, whichever is longer.

A copy of the ATCC deposit receipt is provided herein as Exhibit E.

IV. CONCLUSION

It is submitted that this application is now in good order for allowance and such allowance is respectively solicited. Should the Examiner believe minor matters still remain that can be resolved in a telephone interview, the Examiner is urged to call Applicants' undersigned attorney.

Respectfully submitted,

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APPENDIX A: PARAGRAPHS IN MARKED-UP FORM

Please replace the paragraph at page 2, line 29 – page 3, line 3 with the following paragraph:

One embodiment of the invention consists of a human inflammatory breast cancer xenograft, where the xenograft grows within lymphatic and blood vessel channels, does not express estrogen receptor and progesterone receptor and expresses P53, EGFR, MUC1 and E-cadherin. In a preferred embodiment, the level of E-cadherin expressed by the xenograft is at least two-fold greater than the level of E-cadherin expressed by a noninflammatory breast cancer xenograft. In a related embodiment, the levels of α-catenin and β-catenin expressed by the xenograft are at least two-fold greater than the levels of α-catenin and β-catenin expressed by a noninflammatory breast cancer xenograft. In another related embodiment, the xenograft does not express Her-2/neu. In a highly preferred embodiment the xenograft is the human inflammatory breast carcinoma xenograft designated MARY-X (deposited with the American Type Culture Collection Manassas, Virginia on November 29, 2000, and assigned ATCC Patent Deposit No. PTA-2737). A related embodiment of the disclosed invention consists of an in vitro culture of a human inflammatory breast cancer xenograft, wherein the xenograft grows as a spheroid and can attach to cell monolayers (deposited with the American Type Culture Collection Manassas, Virginia on November 29, 2000, and assigned ATCC Patent Deposit No. PTA-2736). In another related embodiment of the invention, the spheroid disadheres from the cell monolayer when exposed to a culture media containing absent $Ca^{++}$ or anti-E-cadherin antibody. Methods for generating the disclosed xenografts are also described.

Please replace the paragraph at page 22, lines 2-20 with the following paragraph:

Disclosed herein is the first human transplantable inflammatory breast carcinoma xenograft (**MARY-X**). As disclosed below, the xenografts described herein encompass a number of embodiments. One embodiment of the invention consists of a human inflammatory breast cancer xenograft, where the xenograft grows within lymphatic and blood vessel channels, does not express estrogen receptor and progesterone receptor and expresses P53, EGFR, MUC1 and E-cadherin. In a preferred embodiment, the level of E-cadherin expressed by the xenograft is at least two-fold greater than the level of E-cadherin expressed by a noninflammatory breast cancer xenograft. In a related embodiment, the levels of α-catenin and β-catenin expressed by the xenograft are at least two-fold greater than the levels of α-catenin and β-catenin expressed by a noninflammatory breast

cancer xenograft. In another related embodiment, the xenograft does not express Her-2/neu. In a highly preferred embodiment the xenograft is the human inflammatory breast carcinoma xenograft referred to as MARY-X [deposited with ATCC as deposit no. _____ on _____] (deposited with the American Type Culture Collection Manassas, Virginia on November 29, 2000, and assigned ATCC Parent Deposit No. PTA-2737). A related embodiment of the disclosed invention consists of an in vitro culture of a human inflammatory breast cancer xenograft, wherein the xenograft grows as a spheroid and can attach to cell monolayers (deposited with the American Type Culture Collection Manassas, Virginia on November 29, 2000, and assigned ATCC Patent Deposit No. PTA-2736). In a preferred embodiment of the invention, the spheroid disadheres from the cell monolayer when exposed to a culture media containing absent $Ca^{++}$ or anti-E-cadherin antibody.

APPENDIX B: CLAIMS IN MARKED-UP FORM

1. (AMENDED) A human inflammatory breast cancer xenograft, wherein the xenograft grows within lymphatic and blood vessel channels of an immunocompromised host and comprises the following properties:

i) does not express estrogen receptor and progesterone receptor; and

ii) expresses P53, EGFR, MUC1 and E-cadherin.

5. (AMENDED) A human inflammatory breast carcinoma xenograft designated MARY-X and having American Type Culture Collection Accession Number PTA-2737.

12. (AMENDED) The animal model according to claim 10, wherein the human inflammatory breast cancer xenograft, is the xenograft designated MARY-X and having American Type Culture Collection Accession Number PTA-2737.

28. (AMENDED) A method of identifying a molecule whose expression is modulated in inflammatory breast cancer comprising the steps of:

(a) providing a human inflammatory breast cancer xenograft, wherein the xenograft grows within lymphatic and blood vessel channels of an immunocompromised host and has the following properties:

i) does not express estrogen receptor and progesterone receptor; and

ii) expresses P53, EGFR, MUC1 and E-cadherin;

(b) determining the level of expression of at least one molecule in the human inflammatory breast cancer xenograft; and

(c) comparing the level expression of the molecule in the human inflammatory breast cancer xenograft to the level of expression of the molecule in a cell having characteristics which are distinct from the human inflammatory breast cancer xenograft.